REMARKS

In order to simplify prosecution and without acquiescing in any outstanding rejection, article of manufacture claims 14-19 have been canceled herein without prejudice or disclaimer.

SUMMARY OF THE INVENTION

Claim 1 herein is directed to a method for the treatment of a human patient with a disorder characterized by overexpression of ErbB2 receptor, comprising administering a combination of an anti-ErbB2 antibody and gemcitabine, in the absence of an anthracycline derivative, to the human patient in an amount effective to treat the disorder. Claim 37 concerns a method for treating a cancer selected from the group consisting of breast cancer, non-small cell lung cancer (NSCLC), pancreatic cancer and bladder cancer characterized by overexpression of ErbB2 receptor, comprising administering a combination of an anti-ErbB2 antibody and gemcitabine, in the absence of an anthracycline derivative, to a human patient in an amount effective to treat the cancer.

The present application provides actual human clinical data demonstrating that taking into account risk and benefit, an anti-ErbB2 antibody is preferably combined with a chemotherapeutic drug other than an anthracycline derivative (Example 1). The present claims are directed to the selection invention of a combination of the anti-ErbB2 antibody and gemcitabine for human therapy. The preferred indications are breast cancer, non-small cell lung cancer, pancreatic cancer and bladder cancer. Applicants will demonstrate below that the invention is patentable over the cited references.

THE OUTSTANDING REJECTION

The claims are rejected under 35 USC Section 103 over various publications describing (1) combining anti-ErbB2 antibodies with chemotherapeutic agents other than gemcitabine, or (2) various gemcitabine publications, none of which concerns gemcitabine combined with a biologic drug, namely an anti-ErbB2 antibody. The content of the

cited art will be summarized briefly below.

The ErbB2 References

Baselga *et al.*(1997) describes preclinical studies with rhuMoAb HER2 and paclitaxel or doxorubicin (col. 3 on pg. 46); phase II clinical trials combining rhuMoAb HER2 with cisplatin (paragraph bridging pages 46-47); or a planned phase III study of rhuMoAb HER2 combined with adriamycin and cyclophosphamide [AC] or paclitaxel. The combination of an anti-ErbB2 antibody and gemcitabine is not described, let alone treatment of human patients with this combination.

Norton *et al.* (1997) does not teach combining an anti-ErbB2 antibody and gemcitabine, much less treatment of a human patient with the instantly claimed combination. Table 1 referenced by the Examiner refers to HER2 expression in patients treated with paclitaxel or docetaxel (the patients were not treated with an anti-ErbB2 antibody). Col. 1 on S10-9 refers to preclinical studies with 4D5 and paclitaxel; and use of humanized 4D5 as a single agent in patients.

Lippman *et al.* is concerned with a 30kDa glycoprotein that is said to bind to ErbB2. The patent states that the 30kDa ligand may be combined with chemotherapy (col. 27, lines 40-41). This patent does not describe combining an anti-ErbB2 antibody with gemcitabine.

Hynes *et al.* (1994) reports that clinical responses have been seen in patients treated with cisplatin and humanized 4D5 (col. 2 on page 178). The combination of an anti-ErbB2 antibody and gemcitabine for treating human patients is not taught.

Arakawa states that the combination of anti-Her2 antibodies and chemotherapeutic agents has been proposed. The exemplified chemotherapeutic agents are cisplatin and 5-fluorouracil (col. 6, 1st paragraph). This patent does not teach combining an anti-ErbB2 antibody with gemcitabine, much less therapy of human patients therewith.

Hudziak *et al.* teaches anti-ErbB2 antibodies combined with chemotherapy, but does not explicitly describe the presently claimed combination including gemcitabine.

Baselga *et al.* (1996) describes the use of rhuMAb HER2 as a single agent in patients with metastatic breast cancer. In the last paragraph on page 743, Baselga states that in preclinical studies rhuMAb HER2 markedly potentiated the antitumor effects of cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity, and that clinical trials of such combination therapy are currently in progress. There is no discussion of the presently claimed anti-ErbB2 antibody and gemcitabine combination.

Maier *et al.*, Lewis *et al.*, Van Moorsel *et al.* and Hansen do not describe combining an anti-ErbB2 antibody and gemcitabine to treat cancer.

The Gemcitabine References

Clemons *et al.* (1997) describes in Table 8 the use of gemcitabine as a single agent and concludes that gemcitabine looks promising. The combination of gemcitabine and a biologic drug (especially an anti-ErbB2 antibody) is not mentioned or alluded to.

Mosconi *et al.* (1997) reports preliminary results of phase I-II studies of gemcitabine combined with another chemotherapeutic (cisplatin or ifosfamide) in non-small cell lung cancer (NSCLC), rather than with a biologic pharmaceutical (in particular, an anti-ErbB2 antibody).

Carmichael *et al.* (1997) refers to the combination of gemcitabine with doxorubicin or epirubicin. The claims herein exclude combining gemcitabine therapy with co-administration of such anthracycline derivatives.

Carmicheal *et al.* (1995) describes administration of gemcitabine as a single agent, and states that it is an ideal candidate for combination therapy. The suggested drugs to be combined are alkylating agents or

anthracyclines (the latter being excluded by the present claims). See, last paragraph on page 2736 of the reference. There is no mention of the selection invention herein of combining gemcitabine with the anti-ErbB2 antibody biologic.

Tsai *et al.* (1996) describes combining gemcitabine with other chemotherapeutics (cisplatin or etoposide) *in vitro*. The reference does not describe combining gemcitabine with a biologic agent such as an anti-ErbB2 antibody.

The Presently Claimed Invention is Patentable Over the Cited Art

Applicants submit that, prior to the instant application, one could not have predicted the safety and efficacy of the presently claimed selection invention concerning treating human patients with a combination of an anti-ErbB2 antibody and gemcitabine.

Human clinical data has confirmed that the presently claimed combination is safe and effective. See Miller *et al. Oncology* 15(2):38-40 (February, 2001) (of record) which describes preliminary results of a phase II human clinical trial which evaluated the presently claimed gemcitabine and anti-ErbB2 antibody combination with respect to HER2-overexpressing metastatic breast cancer. The combination is well tolerated and appears to be highly active (see abstract of Miller *et al.*). Neither significant cardiac toxicity nor clinical congestive heart failure has been reported to date (1st paragraph in column 1 on page 40 of Miller *et al.*). The lack of significant cardiac toxicity associated with the presently claimed anti-ErbB2 antibody and gemcitibine combination contrasts with the increased cardiac side-effects observed with the anti-ErbB2 antibody and anthracycline derivative combination described at page 47 of the present application.

The present invention is not limited to therapy of metastatic breast cancer. This is demonstrated by Safran *et al. Proc Am. Soc. Clin. Oncol.* 20:130a (2001), of record, which describes Phase II human clinical data in which the presently exemplified anti-ErbB2 antibody (HERCEPTIN®) is

combined with gemcitabine to treat metastatic pancreatic cancer. The abstract states that "Herceptin and gemcitabine have promising activity in an important subset of patients with metastatic pancreatic cancers that overexpress HER-2/*neu*."

The presently claimed combination has further been assessed in patients with HER2 overexpressing, untreated, advanced NSCLC. See Zinner *et al. Proc. Am. Soc. Clin. Oncol.* 20:328a (2001), also of record. Zinner *et al.* note that the regimen is well tolerated, response rates are encouraging, and HERCEPTIN® does not alter gemcitabine clearance.

Hence, Applicants submit that the presently claimed combination of an anti-ErbB2 antibody and gemcitabine is effective and lacks the exacerbated cardiac side effects associated with the anti-ErbB2 antibody and anthracycline derivative combination. These aspects of the presently claimed invention, among other things, are not taught in the cited prior art.

Moreover, Applicants rely on unexpected results as providing objective evidence as to the patentability of the presently claimed combination. In particular, Applicants note that the combination of an anti-ErbB2 antibody (such as HERCEPTIN®) and gemcitabine has been reported to be synergistic. In particular, Nagourney *et al. Breast Cancer Res. Treat.* 57:116 (1999), of record, state that Trastuzumab (the generic name for HERCEPTIN®) enhances the activity of gemcitabine. Bunn *et al.* found additive or synergistic effects between HERCEPTIN® and gemcitabine in NSCLC lines that overexpress HER-2. (No synergy or additive effects were seen with SCLC.) See Bunn *et al. Proc. Am. Assoc. Canc. Res.* 41:719 (2000). Zinner *et al.* note that HERCEPTIN® has been shown to be synergistic with cisplatin and gemcitibine in HER2 overexpressing NSCLC.

The Examiner contends that the relied-upon unexpected results are not unexpected in that it "is well known in the art that HER2 combination therapies exhibit synergy" over a "broad range of combination therapies" and that gemcitabine "produces enhanced cytotoxicity in cells which

overexpress HER2, and is ideal for combination therapy."

Applicants respond that since there was no data in the prior art to indicate that synergy may result from the *selection invention* herein, it is still appropriate to rely on unexpected results.

Moreover, the claimed invention is concerned with therapy of human patients, and the cited art did not provide a prediction that the present combination would be safe and effective *in human patients*, lacking the increased cardiac toxicity seen for the anti-ErbB2 antibody with anthracycline derivative combination.

As to combination therapy with gemcitabine, the prior art is concerned with combining that chemo drug with another chemo drug, rather than a biologic agent, namely anti-ErbB2 antibody as in the claims herein. Hence, Applicants submit that the gemcitabine publications failed to supplement the deficiencies of the ErbB2 references. The cited gemcitabine art did not provide a prediction as to the safety and efficacy of the presently claimed methods of treating human patients.

Hence, Applicants submit that the presently claimed methods are patentable over the cited art. Reconsideration and withdrawal of the Section 103 rejections is respectfully requested.

INFORMATION DISCLOSURE STATEMENT

Applicants point out that the related case (USSN 09/208,649 filed December 10, 1998) has been allowed but suspended for potential interference.

Applicants note that they do not have initialed PTO-1449 forms indicating the following art has been considered by the PTO, and would appreciate it if the Examiner could provide the initialed forms:
IDS hand delivered to the PTO October, 2000 citing ref nos. 65-146.
IDS filed 9/6/2001 citing ref. no. 159.
IDS filed 1/31/2002 citing ref. nos. 160-166.

Serial No.: 09/209,023

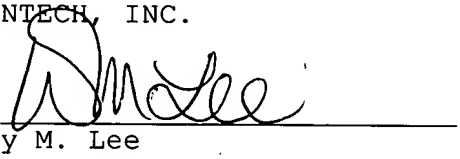
IDS filed 4/10/2002 citing ref. nos. 167-168.

This case is believed to be allowable. If not, the Examiner is respectfully invited to call the undersigned to discuss the case, and thereby expedite prosecution.

Respectfully submitted,

GENENTECH, INC.

Date: May 23, 2002

By: 

Wendy M. Lee
Reg. No. 40,378
Telephone: (650) 225-1994

09157
PATENT TRADEMARK OFFICE

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please cancel claims 14-19, without prejudice or disclaimer.